REMARKS

The Office Action

Claims 1-103 are pending in this application. Claims 1-99, 101, and 103 are withdrawn from consideration. Claims 100 and 102 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description, and under 35 U.S.C. § 112, second paragraph, for indefiniteness. Claim 100 is rejected under 35 U.S.C. § 102(b) for lack of novelty over Sun et al. (J. Biol. Chem. 274:36373-36378, 1999; hereinafter "Sun"). Claim 100 is also rejected under 35 U.S.C. § 103(a) for obviousness over Sun in view of Veronese (U.S. Patent No. 5,286,637; hereinafter "Veronese"), Dalborg (U.S. Patent No. 6,048,720; hereinafter "Dalborg"), Gaertner and Offord (Bioconj. Chem. 7:38-44, 1996; hereinafter "Gaertner"), and Inada et al. (Methods Enzymol. 242:65-90, 1994; hereinafter "Inada"). Finally, the Examiner objects to the specification and drawings due to an improper incorporation by reference, the formatting of trademarks within the specification, and the lack of sequence identifiers in Figures 2, 6, 7, and 9. By this reply, Applicants cancel claims 1-101 and 103, amends claim 102, adds claims 104-109, and addresses each of the rejections.

Support for the Amendment

Support for the amendment to claim 102 and for new claims 104-109 is found in prior claim 100, and in the specification at, e.g., page 30, line 24, through page 31, line 5, page 41, lines 19-27, page 41, line 19, through page 42, line 10, page 70, lines 7-13, and page 83, line 16, through page 84, line 2. SEQ ID NO: 15, which is recited in present claims 102 and 107-109, is directed to the mature Factor XI polypeptide lacking the signal sequence (i.e., amino acids 1-18

of SEQ ID NO: 1); SEQ ID NO: 15 is included in the new sequence listing filed herewith. Applicants note that the numbering system used through the specification corresponds to the amino acid sequence of mature Factor XI and have added this sequence identifier to help clarify the claim language.

Objection to the Specification

The Examiner objects to the specification because it lacks a statement directing the incorporation by reference of materials that Applicants submitted on compact disc at the time of filing. Applicants have amended the specification to include an incorporation by reference statement in compliance with 37 C.F.R. § 1.52. Accordingly, this objection can now be withdrawn.

The Examiner also objects to the presence of trademarks throughout the specification that are not clearly identified as such. Applicants have amended the relevant passages of the specification to clearly identify each trademark. Accordingly, this objection can be withdrawn.

Objection to the Drawings

The Examiner objects to Figures 2, 6, 7, and 9 because these figures, which include nucleic acid and amino acid sequences, do not include sequence identifiers. Applicants provide replacement drawings for Figures 2, 6, 7, and 9 which include a sequence identifier for each of the sequences disclosed. The Examiner also objects to Figure 16 because it includes an incorporation by reference statement. Applicants provide a replacement drawing for Figure 16 which does not include the incorporation by reference statement. Accordingly, the objection to

Figures 2, 6, 7, 9, and 16 can now be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 100 and 102 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. The Examiner states that "the claims are drawn to a myriad of mutant Factor XI proteins or fragments" but the "specific structure of FXI is not described in the claims, e.g., human, mouse, or rat, by a specific structure...The specification and claims lack sufficient number and variety in the type of mutation(s) and sequences of FXI to sufficiently describe the genus" (Office Action, pp. 4-8). Applicants have cancelled claim 100 and has amended claim 102 to specify that the mutations are present at a position relative to the sequence set forth in SEQ ID NO: 15. Accordingly, claim 102 now recites point mutants within a defined sequence set forth in SEQ ID NO: 15. Because the subject matter of claim 102 is now set forth in sufficient detail such that one skilled in the art can clearly conclude that "the inventor invented the claimed invention" (*Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997)), the rejection of claim 102 under 35 U.S.C. § 112, first paragraph, can now be withdrawn.

New claims 104-109 are also set forth in sufficient detail to satisfy the written description requirement of MPEP § 2163. Claim 104 recites a purified Factor XI protein or fragment thereof in which the protein or fragment includes a mutation of a residue that disrupts post-translational N-linked glycosylation when the protein or fragment is recombinantly expressed in an organism; a mutation that eliminates a free, reactive sulfhydryl group of a cysteine residue present in the protein or fragment; or a mutation of the NH_2- or COOH-terminal residue of the protein or

fragment, in which the mutation promotes crystallization of the protein or fragment relative to wild-type Factor XI or a fragment thereof lacking the mutation. Each of these embodiments is described in considerable detail in the present specification.

The Written Description Requirement: The Legal Standard

The written description requirement, as set forth in 35 U.S.C. § 112, first paragraph, requires that the "specification shall contain a written description of the invention." The M.P.E.P. § 2163 states:

> The written description requirement has several policy objectives. "[T]he 'essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." *In re Barker*, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention. See R*egents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089 (1998).

Furthermore, "[t]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention" (M.P.E.P. § 2163).

> An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai*

Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). (M.P.E.P. § 2163; emphasis added.)

Historically, the issue of whether claims pending in an application satisfy the written description requirement was raised in cases where the subject matter at issue, which was to be recited in the claims, was believed to represent "new matter" that was not adequately supported in the original specification or available from the prior art. More recently, though, written description rejections arise in cases where the claimed invention as a whole is thought to not be adequately described, for example, "where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function" (M.P.E.P. § 2163). The prime example of such a situation, described in the M.P.E.P., is an application supporting a claim to a biomolecule sequence, e.g., a nucleic acid or polypeptide sequence. The M.P.E.P. § 2163 states that a biomolecule sequence which is "described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

Applicants' Invention

Applicants' invention, as recited in present claims 104-109, features purified Factor XI proteins and fragments thereof having a mutation of a residue that disrupts post-translational N-linked glycosylation when the protein or fragment is recombinantly expressed in an organism; a

mutation that eliminates a free, reactive sulfhydryl group of a cysteine residue present in the protein or fragment; or a mutation of the NH_2- or COOH-terminal residue of the protein or fragment, in which the mutation promotes crystallization of the protein or fragment relative to wild-type Factor XI or a fragment thereof lacking the mutation. Because the specification discloses a considerable number of Factor XI proteins that fall within claim 104, Applicants clearly show possession of the claimed genus.

Factor XI Glycosylation Mutants

It is known that asparagine residues are post-translationally glycosylated when the asparagine is present within a known glycosylation consensus epitope, the sequence of which is defined as Asn-Xaa-(Ser/Thr), where Xaa is any amino acid except Pro. The specification teaches that one can alter the "residues in the consensus epitope for N-linked glycosylation...[such that] the protein would not be glycosylated" (see, e.g., page 83, lines 20-22, of the specification). Furthermore, it is known that human Factor XI is glycosylated at one of five asparagine residues located within the mature Factor XI protein, e.g., at positions 72, 108, 335, 432, and 473 corresponding to human Factor XI (see, e.g., Yarovaya et al., Biochemistry (Moscow) 67:13-24, 2002; a copy of which is enclosed herewith). The specification teaches that mutations at one or more of these residues produces a mutant Factor XI protein with reduced glycosylation.

For example, the specification teaches that mutation of the serine at position 434 within the human Factor XI protein sequence prevents N-linked glycosylation at the asparagine residue at position 432 (see page 83, line 22, through page 84, line 2). The specification also teaches that

multiple mutations within the Factor XI sequence can be used to produce a mutant Factor XI protein with a profoundly reduced ability to be glycosylated (see page 84, lines 3-8, of the specification). As another example, the specification teaches that the serine residue at position 434 and the threonine residue at position 475 can be mutated to remove the glycosylation consensus epitope, thus producing a mutant Factor XI protein with reduced glycosylation.

In addition, the specification teaches that the rat Factor XI sequence includes two potential N-linked glycosylation sites at Asn^{60} and Asn^{101}, and that mutation of the serine residue at position 62 and the threonine at position 103 within this glycosylation consensus sequence produces a non-glycosylated rat Factor XI protein (see, e.g., page 82, line 24, through page 83, line 2, of the specification). Moreover, both the rabbit and the mouse polypeptide sequences contain glycosylation consensus epitopes corresponding to the epitopes found in the human sequence (see, e.g., Asn^{89}, Asn^{125}, Asn^{352}, Asn^{449}, and Asn^{490} present in the rabbit sequence (SEQ ID NO:2), and Asn^{90}, Asn^{126}, Asn^{355}, Asn^{449}, and Asn^{490} present in the mouse sequence (SEQ ID NO:3)). Each of these consensus epitopes can be altered to produce mutant Factor XI proteins or fragments thereof having reduced glycosylation. Thus, because Applicants' specification clearly teaches a considerable number of species of glycosylation mutants of Factor XI, Applicants clearly show possession of the claimed genus of Factor XI glycosylation mutants.

Factor XI Cysteine Mutants

Claim 104 also encompasses Factor XI mutants that include a mutation that eliminates a free, reactive sulfhydryl group of a cysteine residue. In one embodiment, Applicants' specification teaches:

> The presence of free sulfhydryl groups on FXIcat monomers may also influence solubility, aggregation, and crystallization properties. For

> example, FXIcat has a single cysteine residue (Cys482) that is not involved in a disulfide bond. Cys482 forms a disulfide bond with Cys362 in intact Factor XI and thus is unpaired in the FXIcat. Thus, FXIcat-C482S was generated to replace the free sulfhydryl group with an isosteric serine residue. (Specification, p. 84, line 28, through page 85, line 5.)

Thus, Applicants' specification clearly discloses that unpaired cysteine residues can be eliminated from Factor XI proteins or fragments thereof. Moreover, Applicants point out that human Factor XI, the sequence of which is provided in SEQ ID NO: 1, contains only 36 cysteine residues, while rabbit and mouse Factor XI proteins contain only 34 and 35 cysteine residues, respectively, one or more of which can be eliminated to produce a Factor XI cysteine mutant. Thus, because the sequence of several Factor XI proteins is provided, and because there are only a discreet number of cysteine residues available for mutation, Applicants submit that possession of the claimed genus of Factor XI cysteine mutants has been demonstrated.

Factor XI NH_2- or COOH-Terminal Mutants

Finally, Applicants' specification also discloses that mutations in the amino- and carboxyl-terminal residues of the Factor XI protein or fragment can be prepared. Claim 104 recites that these mutations promote crystallization of the mutant Factor XI protein or fragment thereof relative to the crystallization of wild-type Factor XI or a fragment thereof that lacks the mutation. As an embodiment of this genus, Applicants' specification teaches a Factor XI mutant that lacks the carboxyl-terminal alanine and valine residues (i.e., Ala^{624} and Val^{625} of SEQ ID NO: 1; see, e.g., page 70, lines 7-16, of the specification). Preferred mutations are those that increase solubility, aggregation, and crystallization properties of the mutant Factor XI protein or fragment thereof. Given the teachings in Applicants' specification, such determinations can be

easily made by one who practices in the field of crystallography. Thus, Applicants submit that possession of the genus of Factor XI amino- or carboxyl-terminal mutants has also been demonstrated.

Applicants also note that biological activity of the mutant Factor XI protein or fragment thereof has not been claimed. Thus, the mutant Factor XI proteins and fragments need not demonstrate biological activity.

In summary, a written description of all of the myriad of mutant Factor XI proteins and fragments thereof is not required. For the purposes of written description, all that is required is that Applicants' specification describe the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (M.P.E.P. § 2163; *Regents of the University of California v. Eli Lilly & Co., supra*). Applicants can demonstrate possession by showing that the specification clearly conveys the claimed invention with all of its limitations (*Lockwood v. American Airlines, Inc., supra*). "The description need only describe in detail that which is new or not conventional." (*Hybritech v. Monoclonal Antibodies*, 802 F.2d 1367, at 1384, 231 USPQ 81, at 94 (Fed. Cir. 1986)). For all the reasons discussed above, Applicants respectfully request that the rejection of claims 100 and 102 under 35 U.S.C. § 112, first paragraph, for lack of written description be withdrawn, and that this rejection not be applied to new claims 104-109.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 100 and 102 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. The Examiner states that claim 100 recites "'protein or fragment' in the

preamble, however the mutations are drawn to FXI, not FXI or fragments of FXI, and thus it is unclear how a mutation of a fragment of FXI would alter, e.g. folding of a FXI protein, and thus the claims are indefinite" (Office Action, p. 11, emphasis in original). Applicants have cancelled claim 100 and has addressed this aspect of the rejection in newly added claims 104-109, by reciting in both the preamble and the body of the claims that the mutation is present in both the Factor XI protein and any fragment thereof. This rejection can now be withdrawn and should not be applied to new claims 104-109.

In addition, the Examiner states that the phrase "'enhances the ability' to crystallize" present in claim 100 is indefinite because "'enhancement' is subjective and requires a benchmark from which a comparison can be made" (Office Action, p. 11). As is noted above, claim 100 is cancelled. Thus, the rejection with respect to this claim can be withdrawn. Present claim 102 and newly added claims 104-109 do not contain the phrase pointed out by the Examiner. Accordingly, this rejection can now be withdrawn and should not be applied to present claim 102 or new claims 104-109.

Finally, the Examiner states that "[c]laim 102 is drawn to FXI mutants with specific point mutations[, but it]...is unclear as to which FXI applicant is claiming as the starting point for making the mutants" (Office Action, p. 11). Applicants have amended claim 102 to recite that the FXI protein or fragment thereof includes "one of the following mutations *at a position relative to the sequence set forth in SEQ ID NO: 15*." Accordingly, present claim 102 now recites a starting point for the mutant FXI protein or fragment thereof. This rejection can now be withdrawn.

Rejections under 35 U.S.C. § 102(b)

Claim 100 is rejected under 35 U.S.C. § 102(b) over Sun. The Examiner states:

> Sun teaches that blocks of residues on FXI were substituted by alanine...[and that] [m]utations of any kind will inherently "alter the folding" of a protein, as side chain interactions will be altered. Further, R250A alters the charge of FXI and mutates a residue "that is otherwise post-translationally modified" – that is, a glycosylation site is removed by substitution with alanine26 different FXI mutants.
>
> Sun further teaches mutant 1:FXI [I183A, R184A, D185A] which alters the charge distribution, but not the overall charge, as R and D are oppositely charged amino acids – a net zero charge, which when substituted with A, become neutrally charged – changing the distribution of the charge, but not the overall FXI charge. (Office Action, pp. 11-12.)

Applicants have cancelled claim 100. Thus, the rejection of claim 100 for lack of novelty over Sun can now be withdrawn.

Applicants have also added new claims 104-109 based on prior claim 100. In contrast to prior claim 100, present claims 104-109 do not recite that the Factor XI protein or fragment thereof contains a mutation that enhances the ability of Factor XI catalytic domain to crystallize; a mutation that alters the charge of Factor XI; or a mutation that alters the folding of Factor XI. Instead, present claim 104, from which claims 105-109 depend, recites that the Factor XI protein or fragment thereof includes a mutation of a residue that disrupts post-translational N-linked glycosylation when the protein or fragment is recombinantly expressed in an organism; a mutation that eliminates a free, reactive sulfhydryl group of a cysteine residue; or a mutation of the NH_2- or COOH-terminal residue of the Factor XI protein or fragment thereof that promotes crystallization of the Factor XI protein or fragment relative to wild-type Factor XI or a fragment thereof lacking the mutation. As is discussed below, Sun fails to teach or suggest all of the

elements of present claims 104-109, and thus, the rejection of claim 100 should not be applied to new claims 104-109.

Sun discloses the preparation of recombinant Factor XI proteins containing two, three, or four contiguous alanine substitutions at positions within Ile^{183} to Val^{191}, Ser^{195} to Ile^{197}, and Ser^{258} to Ser^{264} of wild-type Factor XI; these positions fall within a region referred to as the Factor XI "Apple 3 domain" (the "A3 domain"; see abstract of Sun). Sun also discloses the preparation of chimeric Factor XI proteins in which the entire A3 domain or portions thereof are replaced with the corresponding domain or portion from the related plasma protease prekallikrein (PK; see column 2, page 36373 of Sun). None of the Factor XI mutants disclosed by Sun contain a mutation of a residue that disrupts post-translational N-linked glycosylation when the protein or fragment is recombinantly expressed in an organism; a mutation that eliminates a free, reactive sulfhydryl group of a cysteine residue present in the Factor XI protein or fragment thereof; or a mutation of the NH_2- or COOH-terminal residue of the Factor XI protein or fragment thereof that promotes crystallization of the Factor XI protein or fragment relative to wild-type Factor XI or a fragment thereof lacking the mutation, as is recited in present claims 104-109.

The Examiner states that the R250A mutation disclosed by Sun removes a glycosylation site within the mutant Factor XI protein (Office Action, pp. 11-12). This conclusion is in error as arginine residues are not post-translationally glycosylated; glycosylation typically occurs on asparagine residues, as well as on serine and threonine residues. Furthermore, as is discussed above, Factor XI is known to be glycosylated at one of five asparagine residues located within the mature Factor XI protein at positions 72, 108, 335, 432, and 473 (see, e.g., Yarovaya et al., *supra*). Because Sun fails to teach or suggest a Factor XI protein that includes a mutation at any

one of these residues, Sun fails to teach or suggest this element of present claim 104, and claims dependent therefrom.

Sun also fails to teach or suggest the preparation of a Factor XI protein that includes a mutation that eliminates a free, reactive sulfhydryl group of a cysteine residue. All of the Factor XI mutants prepared by Sun include the cysteine residues present in the wild-type Factor XI protein. Thus, Sun fails to teach or suggest this element of present claim 104, and claims dependent therefrom. Finally, Sun fails to teach or suggest the preparation of a Factor XI protein that includes a mutation of the NH_2- or COOH-terminal residue of mature Factor XI. The Factor XI mutants disclosed by Sun include mutations present only within the A3 domain (i.e., amino acids 183-191, 195-197, and 258-264); the mutations are not present at the amino- or carboxyl-terminus of Factor XI. Accordingly, Sun fails to teach or suggest this element of present claim 104, and claims dependent therefrom, as well.

For all the reasons discussed above, Applicants submit that Sun fails to teach or suggest all of the elements of new claims 104-109. Accordingly, the rejection of prior claim 100 should not be applied to new claims 104-109.

Rejections under 35 U.S.C. § 103(a)

Claim 100 is rejected under 35 U.S.C. § 103(a) over Sun in combination with Veronese, Dalbourg, Gaertner, and Inada. As is discussed above, Applicants have cancelled claim 100. Thus, the rejection of claim 100 for obviousness over Sun in combination with Veronese, Dalbourg, Gaertner, and Inada can now be withdrawn. Furthermore, the rejection of claim 100 over the combination of Sun, Veronese, Dalbourg, Gaertner, and Inada should not be applied to

new claims 104-109. None of Sun, Veronese, Dalbourg, Gaertner, or Inada, either singly or in combination, teaches or suggests a purified Factor XI protein or fragment thereof that contains a mutation of a residue that disrupts post-translational N-linked glycosylation when the protein or fragment is recombinantly expressed in an organism; a mutation that eliminates a free, reactive sulfhydryl group of a cysteine residue; or a mutation of the NH_2- or COOH-terminal residue of the Factor XI protein or fragment thereof that promotes crystallization of the Factor XI protein or fragment relative to wild-type Factor XI or a fragment thereof lacking the mutation.

The Examiner states:

> It would have been obvious to one of ordinary skill in the art at the time of the invention to have PEGylated the FXI, generating a "mutation of the N- or C- terminus residue", because PEGylation increases the biological half-life and retain[s] the biological activity of the peptides to which they are attached ("inhibiting proteolytic activity is better sustained throughout time"), as taught by Dalbourg and Gaertner.
>
> One of ordinary skill in the art would have had a reasonable expectation for success in making the PEGylated FXI, as PEGylation of peptides is a routine technique widely practiced in the peptide arts...as taught by Dalbourg, Gaertner, Inada, and Veronese. (Office Action, p. 15.)

Applicants respectfully disagree.

Sun is discussed *supra*. Moreover, the Examiner acknowledges that Sun does not teach or suggest a purified Factor XI protein or fragment thereof that has a mutation at the amino- or carboxyl-terminus, as is recited in new claim 104, and claims dependent therefrom (Office Action, p. 13). Therefore, to support the rejection the Examiner relies on Gaertner, Veronese, Dalbourg, and Inada for their disclosure of protein modification by PEGylation, which the Examiner states would be a desirable modification because PEGylation increases the solubility of

the protein in both aqueous and organic solvents, increases the half-life and clearance time, reduces both antigenicity and immunogenicity, and improves resistance to proteolysis, while retaining biological activity of the Factor XI (Office Action, p. 15). Applicants note that new claim 104 requires that the mutation of an amino- or carboxyl-terminal residue of Factor XI protein or fragment thereof promote *crystallization* of the Factor XI protein or fragment relative to wild-type Factor XI or a fragment thereof lacking the mutation. While PEGylation of proteins can enhance certain biological effects of proteins, as is discussed by Veronese, Dalbourg, Gaertner, and Inada, PEGylation of Factor XI or a fragment thereof would not promote the formation of crystals of Factor XI or a fragment thereof for use in crystallography.[1] PEGylation, in fact, produces the opposite result by increasing the heterogeneity of the polypeptide to which it is attached, which prevents the generation of protein crystals that can be used to successfully solve its crystal structure by crystallography. This heterogeneity occurs due to random modification of the polypeptide sequence by PEG moieties (100% PEGylation rarely occurs), as well as by modification by PEG moieties having different molecular weights. Because the formation of protein crystals requires that the polypeptide be capable of efficient packing, which cannot occur following PEGylation, the modification of Factor XI by PEGylation would hinder rather than promote the formation of crystals. For this reason, the combination of Sun, Gaertner, Veronese, Dalbourg, and Inada fails to teach or suggest all elements of present claim 104, and claims dependent therefrom.

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1 Applicant notes that PEGylation, the covalent attachment of a PEG moiety to a residue of a polypeptide sequence, should not be confused with the use of PEG as a precipitant during the preparation of crystals for crystallography studies, in which the PEG can be present in solution as a precipitant. In this situation, the PEG moiety is not covalently attached to the polypeptide chain.

Applicants also note that the term "mutation," as it is known in the art and used in the present specification, refers to changes that result in a substitution, deletion, or addition of one or more amino acid within the polypeptide chain of Factor XI or a fragment thereof. In contrast, the term "modification" refers to a covalent chemical change to one or more residues within a polypeptide chain; it does not refer to a substitution, deletion, or addition of one or more amino acids. Thus, the term "mutation" in present claim 104 does not encompass covalent modifications, such as PEGylation. For this reason as well, the combination of Sun, Veronese, Dalbourg, Gaertner, and Inada does not teach or suggest all elements of present claims 104-109.

Because none of Sun, Veronese, Dalbourg, Gaertner, and Inada teaches or suggests a purified Factor XI or fragment thereof having a mutation of an amino- or carboxyl-terminal residue that promotes *crystallization* of the Factor XI protein or fragment relative to wild-type Factor XI or a fragment thereof lacking the mutation, as is recited by present claim 104, and claims dependent therefrom, the references, either singly or in combination, fail to teach or suggest all elements of present claims 104-109. Thus, the rejection of claim 100 under 35 U.S.C. § 103(a) over the combination of Sun, Veronese, Dalbourg, Gaertner, and Inada should not be applied to new claims 104-109.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is requested.

Enclosed is a Petition to extend the period for replying for three months, to and including February 6, 2006, as February 5, 2006, fell on a Sunday, and a check in payment of the required extension fee. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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